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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KINSEY WHITE, NICOLE ERIN	
ART UNIT	**PAPER NUMBER**
1648	
MAIL DATE	**DELIVERY MODE**
03/12/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/743,338	KAPIKIAN ET AL.	
	Examiner	Art Unit	
	NICOLE KINSEY WHITE	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 December 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,7-27 and 29-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-27 and 29-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5 and 15 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is maintained for reasons of record.

Applicants state that a Declaration will be provided assuring public availability of the deposited material when allowable subject matter has been indicated. The rejection will be maintained until the assurance is obtained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2142.

Claims 1-4, 7-14, 16-27 and 29-34 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Midthun et al. (Journal of Virology, 1985, 53(3): 949-954), designated Midthun '85, Midthun et al. (Journal of Clinical Microbiology, 1986, 24(5): 822-826), designated Midthun '86, Hoshino et al. (Journal of Medical Virology, April 1997, 51: 319-325), Clark et al. (U.S. Patent No. 6,113,910) and Clark et al. (J. Infect. Dis., 1990, 161(6):1099-104).

The claims are primarily drawn to a multivalent immunogenic composition comprising at least four bovine strain reassortant rotaviruses and a physiologically acceptable carrier, wherein each bovine reassortant rotavirus comprises a single rotavirus VP7 gene that encodes a protein that is immunologically cross-reactive with an antigenically distinct human VP7 serotype and the remaining 10 genes derived from the bovine UK strain, and wherein the composition induces an effective immunogenic response to each antigenically distinct human rotavirus VP7 serotype without causing a transient low level fever in a statistically significant number of vaccinees when each of the rotavirus reassortant serotype is administered at a dosage of less than $10^{6.0}$ plaque forming units.

Midthun et al. '85 and '86 teach four human x bovine reassortant rotaviruses where the reassortants have one human gene (D (serotype 1), DS-1 (serotype 2), P (serotype 3) and ST3 (serotype 4)) from a human rotavirus serotype and where the bovine parent/backbone, which is the UK strain, provides the remaining 10 genes (see, for example, Midthun '85 introduction). Both references produce the human x bovine reassortants for vaccine purposes (i.e., administering the human x bovine reassortants as vaccines to induce an immune response).

Neither Midthun et al. '85 nor Midthun '86 teaches a multivalent immunogenic composition of four reassortant rotaviruses, a physiologically acceptable carrier, induction of an immunogenic response without causing a low level fever, or a dosage.

However, Clark et al. teaches combining different human x bovine reassortant rotaviruses into a single composition (see col. 7, lines 39-63). Clark et al. states "[t]he

vaccine compositions of the invention may desirably include other rotavirus reassortants of the invention, in addition to a G1 reassortant. . . . This composition has been shown to elicit a stronger immune response than does a single reassortant rotavirus containing both the human v.p.4 and the human v.p.7 (encoded by gene segment 9). . . . . Suitable combination vaccines, which may be univalent, bivalent, trivalent, quadrivalent, quinquavalent or sexavalent may include various combinations of the G1, G2, G3, G4, P1 and P2 reassortants. Other suitable reassortants of the invention may be selected for use in vaccine compositions other than those specified in Table 2 by reference to Table 1 above and the present specification." Clark et al. also teaches suitable carriers (see col. 7, lines 64-66), liquid dose forms (see col. 7, lines 66-67), buffers (see col. 8, line 1), lyophilized forms (see col. 8, lines 2-4), adjuvants (see col. 8, lines 15-17), multiple administrations (see, for example, col. 8, lines 47-52) and methods for stimulating the immune system (see, for example, Example 4). Clark et al. further teaches a general dose range between 10^6 and 10^9 and other dosages of $10^{5.5}$, $10^{6.5}$ and $10^{7.5}$.

Clark et al. (J. Infect. Dis.) discloses the safety and protective efficacy of a serotype 1 reassortant of bovine rotavirus, which contains a gene segment 9 coding for the surface structural protein vp7 of a human serotype 1 rotavirus, with all other gene segments derived from WC3 rotavirus, which had previously been shown to be safe and immunogenic in infants. Infants 2-11 months of age were given two doses of vaccine ($10^{7.3}$ plaque-forming units/dose) or of placebo 28 days apart. Adverse reactions to the vaccine were not detected. The incidence of serum plaque reduction neutralization

antibody responses to two doses of vaccine was serotype 6, 97%; serotype 3, 68%; and serotype 1, 22%. Active surveillance during the subsequent rotavirus season revealed 8 cases of rotavirus gastroenteritis in 39 placebo control infants and no cases in 38 WI79-9 vaccine recipients (protection = 100%).

Hoshino et al. teaches that the four human serotypes (serotypes 1-4, also disclosed in Midthun et al. '85 and '86) are the most epidemiologically important serotypes (see abstract).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Midthun et al. '85 and '86 to produce a multivalent composition with two, three, four, five, six, etc. reassortants. One would have been motivated to do so given the numerous teachings of Clark et al., in particular, the teaching to produce a multivalent composition of reassortants and to include more than one reassortant to elicit a stronger immune response (see col. 7 lines 43-49) and the teachings of Hoshino et al. There would have been a reasonable expectation of success given the fact that it is common and routine to produce multivalent vaccines and given the knowledge that Clark et al. successfully vaccinated subjects with reassortant vaccines (see Examples) and also given the knowledge that WC3 strain of Clark et al. and the UK strain are of the same serotype (serotype 6) and both have been used as human x bovine reassortants to vaccinate subjects. Finally, the prior art references, when combined, teach or suggest all the claim limitations. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

As for the number of components in the vaccine composition and dosages claimed, it is well within the purview of one of ordinary skill in the vaccine art to optimize dosages recited in the claims. According to section 2144.05 of the MPEP, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.")

A particular parameter must first be recognized as a result-effective variable, i.e., a variable, which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977). In the instant application, the dosages taught by Clark et al. (10^6-10^9 and $10^{5.5}$, $10^{6.5}$ and $10^{7.5}$) produced a recognized result (i.e., neutralizing antibodies, see Example 4 where Clark et al. states "30 of 54 infants, or 57%, given <u>any</u> dose of vaccine developed a virus-neutralizing serum antibody response to one or more of rotavirus serotypes G1, G3, or bovine." *emphasis added*). The doses Clark et al. refers to are $10^{5.5}$, $10^{6.5}$ and $10^{7.5}$. Therefore,

determining other optimum or workable dosages or reassortants to include in a multivalent composition is routine experimentation.

Further, it would have been obvious for one of ordinary skill in the vaccine arts to administer the human x bovine reassortants to infants of less than six months of age in view of the teachings of Clark et al. (J. Infect. Dis.) (serotype 1 bovine rotavirus reassortant provided 100% protection for vaccinated infants age 2-11 months).

With regard to citrate buffer, none of the references teach constituting the vaccine in citrate buffer. However, conventional pharmaceutical carriers are obvious alternatives to one another for one of ordinary skill in the art.

Response to Applicants' Arguments

In the reply dated December 21, 2009, applicants made several arguments. Each argument has been fully considered and addressed below.

The Office has not addressed claims 22-34

Claims 22-34 are directed to a method for stimulating the immune system of an infant of less than six months of age by administering the bovine reassortants of claims 1-21.

As stated above, both Midthun references produced human x bovine reassortants for vaccine purposes (i.e., administering the human x bovine reassortants as vaccines to induce an immune response). Further, Clark et al. teaches the administration of human x bovine reassortants. Furthermore, it is well known in the art

to administer human x bovine reassortants as vaccines. Therefore, it would be obvious to administer the claimed human x bovine reassortants to induce an immune response.

No reasonable expectation of success

Applicants next argue that there is no reasonable expectation of success in producing a multivalent composition with 2-5 reassortants that would induce an effective immune response in infants of less than six months of age without causing a transient low level fever. Again, this argument has been fully considered and not found persuasive in view of the teachings of the prior art.

As stated previously, Clark et al. is cited, *inter alia*, for teaching several doses of human x bovine reassortants including a general dose range between 10^6 and 10^9 and other dosages of $10^{5.5}$, $10^{6.5}$ and $10^{7.5}$. Clark et al. found that no vaccine associated symptoms of disease were observed (see Example 4, lines 55-56). Further, Clark et al. states that "30 of 54 infants, or 57%, given any dose of vaccine developed a virus-neutralizing serum antibody response to one or more of rotavirus serotypes G1, G3, or bovine." *emphasis added*). The "any dose" Clark et al. refers to includes the $10^{5.5}$ dose (see Example 4). Therefore, contrary to applicants' argument, the $10^{5.5}$ dose of Clark et al. was effective and provides a reasonable expectation of success for the $10^{5.5}$ dose and other doses of human x bovine reassortants. Clark et al. provides data regarding "any dose," which includes the $10^{5.5}$ dose. There is no mention of any dose that produced no neutralizing serum antibodies. Clark et al. provides doses, number of subjects, the ages of the subjects (for the doses $10^{5.5}$ and $10^{6.5}$), guidance and data

such that one of ordinary skill in the art can reproduce the experiment at the given doses with the expectation of success. Furthermore, because the following trial in Example 5 of Clark et al. used a higher dose ($10^{7.3}$), it does not indicate that the previous dose of $10^{5.5}$ was ineffective. Thus, the combined teachings of Midthun '85, Midthun '86, Clark et al. and Clark et al. (J. Infect. Dis.) teach the claimed invention (an immunogenic composition comprising at least four human x bovine (UK) reassortants) as outlined above.

Clark et al. has no support for a single gene substitution

Clark et al. used the WI79-3,9 reassortant in the study mentioned above (Example 4). WI79-3,9 contains human gene segments 3 and 9 from strain WI79. While this is not a single reassortant, it still falls within the scope of applicants claims, which recite "wherein the bovine reassortant rotavirus comprises a single VP7 gene." The open language "comprising" allows for the addition of other genes. Even if the claim were to recite "consisting of," it is still obvious and routine to use a single gene given the teachings in the prior art, as outlined above.

Clark et al. only successfully vaccinated subjects at a concentration over 10^7 pfu

Applicants next argue that Clark et al. only successfully vaccinated subjects with bovine WC3 x human VP7 G1 serotype at a concentration over 10^7 pfu.

As stated previously, Clark et al. is cited, *inter alia*, for teaching several doses of human x bovine reassortants including a general dose range between 10^6 and 10^9 and

other dosages of $10^{5.5}$, $10^{6.5}$ and $10^{7.5}$. Further, Clark et al. states that "30 of 54 infants, or 57%, given any dose of vaccine developed a virus-neutralizing serum antibody response to one or more of rotavirus serotypes G1, G3, or bovine." *emphasis added*). The "any dose" Clark et al. refers to includes the $10^{5.5}$ dose (see Example 4). Therefore, contrary to applicants' argument, the $10^{5.5}$ dose of Clark et al. was effective and provides a reasonable expectation of success for the $10^{5.5}$ dose and other doses of human x bovine reassortants. Clark et al. provides data regarding "any dose," which includes the $10^{5.5}$ dose. There is no mention of any dose that produced no neutralizing serum antibodies. Clark et al. provides doses, number of subjects, the ages of the subjects (for the doses $10^{5.5}$ and $10^{6.5}$), guidance and data such that one of ordinary skill in the art can reproduce the experiment at the given doses with the expectation of success. Furthermore, because the following trial in Example 5 of Clark et al. used a higher dose ($10^{7.3}$), it does not indicate that the previous dose of $10^{5.5}$ was ineffective.

Further, assuming *arguendo*, that Clark et al. et al. did not vaccinate infants less than 6 months of age, it does not preclude that fact that it would be obvious to one of ordinary skill in the art to vary the dose of vaccine depending on the subject. For example, it would be obvious to administer lower doses of vaccine to infants given the fact that infants are smaller than adults (vaccine doses are determined by body mass or weight). Further, it would be obvious to administer lower doses of vaccine to decrease the number of side effects, if there are any.

Thus, the combined teachings of Midthun '85, Midthun '86, Clark et al. and Clark et al. (J. Infect. Dis.) teach the claimed invention (an immunogenic composition comprising at least four human x bovine (UK) reassortants) as outlined above.

No reason to believe bovine strain WC3 and UK would induce the same or similar immune response

Applicants next argue that there is no reason to believe bovine strains WC3 and UK would induce the same or similar immune response. Again, this argument has been fully considered and not found persuasive in view of the teachings of the prior art.

As stated previously, it is well known that the WC3 strain of Clark et al. and the UK strain are of the same serotype (see, for example Gouvea et al. (Journal of Clinical Microbiology, 1994, 32(5): 1338-1340). The definition of serotype is: A group of organisms, microorganisms, or cells distinguished by their shared specific antigens as determined by serologic testing (see any online dictionary such as dictionary.com). Further, Midthun et al. (Clinical Microbiology Reviews, 1996, 9(3):423-434) discloses that "the VP4 specificity by neutralization of WC3 has not been reported, but with regard to genotype, it appears to be similar to UK virus . . . . (see page 427). Therefore, based on these teachings, it is **reasonable** for one of ordinary skill in the art to expect that the UK strain used in Midthun '85 and '86 would behave similarly as the WC3 strain. Further, Midthun et al. '85 states "[t]he single human rotavirus gene substitution reassortants described in this study represent potential vaccine candidates. The major neutralization protein of these reassortants is derived from the human rotavirus parent,

and these viruses should therefore have the desired immunogenicity. It is also likely that the presence of 10 animal rotavirus genes in these reassortants will render such viruses attenuated for humans. This latter supposition is supported by the fact that bovine rotavirus UK and RRV have been administered to susceptible volunteers with a low level of serum antibodies and did not produce illness (Kapikian et al., in press; Wyatt et al., in press). These findings suggest that single human rotavirus gene substitution reassortants may be promising vaccine candidates for use in prevention of human rotavirus disease." Emphasis added. The reassortants described in the Midthun et al. studies were based on the UK strain. Therefore, it is reasonable to believe that the UK strain can be substituted in the for WC3 in human x bovine reassortants. Finally, it is well known in the art that both WC3 and UK strains of bovine rotavirus have been used to vaccinate subjects.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571) 272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648